Mitral annular calcification in the elderly - Quantitative assessment

Eberhard, M ; Schönenberger, A L N ; Hinzpeter, R ; Euler, A ; Sokolska, J ; Weber, L ; Kuzo, N ; Manka, R ; Kasel, A M ; Tanner, F C ; Alkadhi, H

Abstract: PURPOSE: To determine the reliability of subjective and objective quantification of mitral annular calcification (MAC) in elderly patients with severe aortic stenosis, to define quantitative sex- and age-related reference values of MAC, and to correlate quantitative MAC with mitral valve disease. METHODS: In this retrospective, IRB-approved study, we included 559 patients (268 females, median age 81 years, inter-quartile range 77-85 years) with severe aortic stenosis undergoing CT. Four independent readers performed subjective MAC categorization as follows: no, mild, moderate, and severe MAC. Two independent readers performed quantitative evaluation of MAC using the Agatston score method (Agatston_{MAC}). Mitral valve disease was determined by echocardiography. RESULTS: Subjective MAC categorization showed high inter-reader agreement for no ($k = 0.88$) and severe MAC ($k = 0.75$), whereas agreement for moderate ($k = 0.59$) and mild ($k = 0.45$) MAC was moderate. Intra-reader agreement for subjective MAC categorization was substantial ($k = 0.69$ and 0.62). Inter- and intra-reader agreement for Agatston_{MAC} were excellent (ICC = 0.998 and 0.999, respectively), with minor inconsistencies in MAC involving the left ventricular outflow tract/aortic valve. There were significantly more women than men with MAC (n = 227, 85% versus n = 209, 72%; $p < 0.001$), with a significantly higher Agatston_{MAC} (median 597, range 81-2055 versus median 244; range 0-1565; $p < 0.001$), particularly in patients 85 years of age. Agatston_{MAC} showed an area-under-the-curve of 0.84 to diagnose mitral stenosis, whereas there was no association of Agatston_{MAC} with mitral regurgitation ($p > 0.05$). CONCLUSIONS: Our study in elderly patients with severe aortic stenosis shows that quantitative MAC scoring is more reliable than subjective MAC assessment. Women show higher Agatston_{MAC} scores than men, particularly in the elderly population. Agatston_{MAC} shows high accuracy to diagnose mitral stenosis.

DOI: https://doi.org/10.1016/j.jcct.2020.06.001

Originally published at:
Eberhard, M; Schönenberger, A L N; Hinzpeter, R; Euler, A; Sokolska, J; Weber, L; Kuzo, N; Manka, R; Kasel, A M; Tanner, F C; Alkadhi, H (2021). Mitral annular calcification in the elderly - Quantitative assessment. Journal of Cardiovascular Computed Tomography, 15(2):161-166.

DOI: https://doi.org/10.1016/j.jcct.2020.06.001

ARTICLE IN PRESS

Journal of Cardiovascular Computed Tomography xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.elsevier.com/locate/jcct

Mitral annular calcification in the elderly – Quantitative assessment

M. Eberhard[a,*], A.L.N. Schönenberger[a], R. Hinzpeter[a], A. Euler[a], J. Sokolska[b,c], L. Weber[a], N. Kuzo[b], R. Manka[a,b], A.M. Kasel[b], F.C. Tanner[b], H. Alkadhi[a]

[a] Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, University of Zurich, Switzerland
[b] Department of Cardiology, University Heart Center Zurich, Zurich, Switzerland
[c] Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland

ARTICLE INFO

Keywords:
Aged
80 and over
Calcification
Mitral valve
Mitral valve stenosis
Computed tomography

ABSTRACT

Purpose: To determine the reliability of subjective and objective quantification of mitral annular calcification (MAC) in elderly patients with severe aortic stenosis, to define quantitative sex- and age-related reference values of MAC, and to correlate quantitative MAC with mitral valve disease.

Methods: In this retrospective, IRB-approved study, we included 559 patients (268 females, median age 81 years, inter-quartile range 77–85 years) with severe aortic stenosis undergoing CT. Four independent readers performed subjective MAC categorization as follows: no, mild, moderate, and severe MAC. Two independent readers performed quantitative evaluation of MAC using the Agatston score method ($Agatston_{MAC}$). Mitral valve disease was determined by echocardiography.

Results: Subjective MAC categorization showed high inter-reader agreement for no ($k = 0.88$) and severe MAC ($k = 0.75$), whereas agreement for moderate ($k = 0.59$) and mild ($k = 0.45$) MAC was moderate. Intra-reader agreement for subjective MAC categorization was substantial ($k = 0.69$ and 0.62). Inter- and intra-reader agreement for $Agatston_{MAC}$ were excellent (ICC = 0.998 and 0.999, respectively), with minor inconsistencies in MAC involving the left ventricular outflow tract/aortic valve. There were significantly more women than men with MAC (n = 227, 85% versus n = 209, 72%; $p < 0.001$), with a significantly higher $Agatston_{MAC}$ (median 597, range 81–2055 versus median 244; range 0–1565; $p < 0.001$), particularly in patients ≥85 years of age. $Agatston_{MAC}$ showed an area-under-the-curve of 0.84 to diagnose mitral stenosis, whereas there was no association of $Agatston_{MAC}$ with mitral regurgitation ($p > 0.05$).

Conclusions: Our study in elderly patients with severe aortic stenosis shows that quantitative MAC scoring is more reliable than subjective MAC assessment. Women show higher $Agatston_{MAC}$ scores than men, particularly in the elderly population. $Agatston_{MAC}$ shows high accuracy to diagnose mitral stenosis.

1. Introduction

Mitral annular calcification (MAC) is a chronic degenerative process of the fibrous support structure of the mitral valve.[1,2] The reported prevalence of MAC is about 8% in an unselected, general population[3] and increases with age, in the presence of cardiovascular risk factors, and with chronic kidney dysfunction.[4,5]

MAC is usually asymptomatic. However, the presence of MAC has been associated with a higher risk of cardiovascular events and mortality, conduction abnormalities, and mitral valve disease.[5–9] In addition, extensive MAC represents a challenge for surgery when mitral valve repair or replacement is planned.[10] On the contrary, extensive and circumferential MAC can act as an anchor for positioning balloon-expandable valves in the mitral position.[11–13]

Computed tomography (CT) enables the accurate and reproducible assessment of cardiac calcifications, including the coronary arteries and aortic valve.[3,14–16] All studies evaluating the prognostic effect of MAC on outcome so far applied a subjective, semi-quantitative scoring system of MAC on contrast-enhanced CT using different methods.[5,6,17,18] For example the method described by Amat-Santos et al.[5,18] used a 4-grade scoring system evaluating the circumferential involvement of the mitral annulus, whereas involvement of ≥1/2 of the circumference represents severe MAC. Ancona et al.[6] used a 5-grade scoring system evaluating the extent of posterior involvement as grade 0–3 and extension to the anterior annulus as grade 4. Takana et al.[17] also used a 5-grade scoring system with grades representing the involvement of 0, < 1/4, < 1/2, < 3/4 and > 3/4 of the entire annular circumference.

* Corresponding author. Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Raemistrasse 100, CH-8091, Zurich, Switzerland.
E-mail address: matthias.eberhard@usz.ch (M. Eberhard).

https://doi.org/10.1016/j.jcct.2020.06.001
Received 1 April 2020; Received in revised form 4 May 2020; Accepted 1 June 2020

Interestingly, echocardiography employs a semi-quantitative grading scheme similar to that from Amat-Santos et al. for CT.[2,18] Alternatively, the severity of MAC can be assessed with echocardiography by measuring the maximal MAC thickness from the leading to the trailing edge.[9] A drawback of all these methods are their subjectivity, and the categorization of MAC by different readers is most likely prone to considerable intra- and inter-reader variability.

The aim of our study was (1) to determine the reliability of subjective and objective quantification of MAC in elderly patients with severe aortic stenosis, (2) to define quantitative sex- and age-related reference values of MAC quantification using the Agatston score method, and (3) to correlate quantitative MAC with mitral valve disease.

2. Material and methods

2.1. Patient population

Baseline data collection was performed on the basis of a nation-wide prospective registry (SWISS TAVI Registry). This study had local institutional and ethics committee approval. All patients provided written informed consent.

Between November 2008 and May 2019, we screened 1′736 consecutive patients with severe aortic stenosis undergoing CT as part of the institutional pre-procedural protocol prior to transcatheter aortic valve replacement (TAVR). Only patients undergoing non-enhanced CT were included in this study (n = 564). Five patients with previous mitral valve replacement/repair were excluded. Finally, a total of 559 patients (268 females, 291 males, median age 81 years, inter-quartile range 77–85 years) were included in this study. Patient demographics, cardiovascular risk factors, medical history, and echocardiographic findings were noted for each patient.

2.2. CT data acquisition and image reconstruction

All patients underwent CT on either a second or third generation dual-source CT scanner (SOMATOM Force; SOMATOM Definition Flash; Siemens Healthineers, Forchheim, Germany). Prospectively electrocardiography (ECG)-gated non-enhanced CT was performed in a sequential mode at 70% of the RR interval at a tube voltage of 120 kVp. Reconstruction parameters were as follows: slice thickness, 3 mm; increment, 1.5 mm; reconstruction kernel, soft tissue convolution kernel; filtered back projection as recommended for aortic valve and coronary artery calcium scoring.[19] Then, prospectively ECG-gated high-pitch CT angiography of the thoracoabdominal aorta was performed with our default protocol using a patient-dependent contrast media volume (iopromide, Ultravist®, 370 mg/mL; Bayer HealthCare, Berlin, Germany) as described before.[20]

2.3. Subjective MAC assessment

Four blinded and independent readers ([J.S.], [L.W.], [A.E.] and [M.E.]) with 2, 5, 6, and 7 years of experience in cardiovascular imaging were instructed to semi-quantitatively assess MAC according to the method described by Amat-Santos et al.[18] MAC was grouped into four categories and severity was determined by the circumferential involvement of the mitral ring. No MAC; mild MAC: involvement of less than one-third of the annulus; moderate MAC: involvement between one-third and half of the mitral annular circumference; severe MAC: calcification of more than half of the mitral annular circumference.

Using the 3D tool of a dedicated post-processing software (3mensio Structural Heart 7.3, Pie Medical Imaging, Maastricht, The Netherlands), readers were instructed to create multiplanar views including axial and double oblique views at the mitral annular level as average intensity projections or maximal intensity projections at their own discretion to assess MAC (Fig. 1, Panel A–C). After evaluating five cases together (being not part of this study) readers evaluated cases independent from each other. One reader evaluated all patients and three readers evaluated 400 cases to determine inter-reader agreement. Two readers performed a second readout of 200 randomly selected cases to assess intra-reader agreement. This readout was performed one month after the initial assessment in order to avoid recall bias.

2.4. Objective, quantitative MAC assessment

Two other independent readers ([A.S.], [R.H.]) not involved in the subjective readout and with 3 and 4 years of experience in cardiovascular imaging quantified MAC on axial slices using a commercially available post-processing platform (3mensio Structural Heart 7.3, Pie Medical Imaging, Maastricht, The Netherlands) (see Fig. 1, Panel D–F). One reader performed a second readout of 400 randomly selected cases to determine intra-reader agreement.

The software automatically detects pixels ≥130 Hounsfield Units (HU), and observers marked each calcified lesion at the base of mitral leaflets between the left atrium and ventricle by carefully placing regions-of-interest (ROI) and excluding calcification of the mitral leaflets, left ventricular outflow tract, aortic valve and/or the coronaries. The Agatston scores for individual calcifications of the mitral annulus were added to derive the total Agatston score of the mitral annulus ($Agatston_{MAC}$).

2.5. Echocardiography

Using commercially available ultrasound systems transthoracic echocardiography was performed before valve replacement. Images were acquired according to current guidelines and analyzed offline by certified staff members. The degree of mitral regurgitation and mitral stenosis was assessed using structural, spectral, and colour-Doppler images and were graded as mild, moderate, or severe using multi-parametric assessments according to the European Association of Echocardiography/American Society of Echocardiography recommendations.[21,22] According to Okuno et al. relevant mitral valve disease was considered in the presence of moderate or severe mitral regurgitation or mild, moderate or severe mitral stenosis.[4]

2.6. Statistical analysis

Non-parametric, continuous variables are presented as median values with interquartile ranges (IQR) and were compared with the Mann-Whitney-U test. To compare subjective MAC assessment between readers multireader Fleiss' kappa analysis was performed. According to Landis and Koch, the level of agreement for overall subjective analysis and analysis of individual categories were categorized as almost perfect ($k > 0.8$), substantial ($k = 0.6–0.8$) and moderate ($k = 0.4–0.6$).[23] Inter- and intrareader agreement for $Agatston_{MAC}$ was evaluated using intraclass correlation coefficients (ICC). According to Rosner, an ICC > 0.75 was categorized as excellent.[24] Receiver operatic characteristics (ROC) analysis was performed to determine the area-under-the-curve (AUC) with a 95% confidential interval (95% CI) for $Agatston_{MAC}$ and subjective MAC assessment to diagnose mitral stenosis and regurgitation. Youden's index was applied to derive a cut-off value with high sensitivity and specificity.

All analyses were performed using commercially available software (SPSS 26, IBM Corporation, Armonk, NY, USA). A two-tailed $p < 0.05$ was considered to infer statistical significance.

3. Results

Baseline characteristics of our study cohort are provided in Table 1. 134 patients had relevant mitral regurgitation (24%) and 25 patients had mitral stenosis (4%).

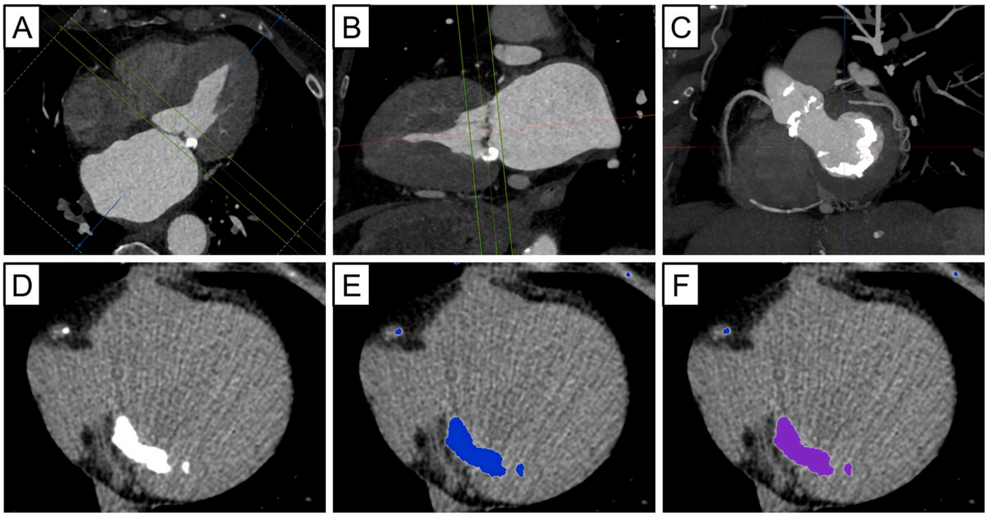


Fig. 1. Semi-quantitative and quantitative MAC assessment. Panels A–C illustrate subjective MAC assessment using a dedicated software tool. Rotation of crosshairs (A, B) enables the multiplanar assessment of the mitral annulus (C) with average intensity projections or maximum intensity projections (C). Panels D–F illustrate quantitative MAC assessment. Panels E and F show the post-processing for calcium quantification using a semi-automated software tool with automatic detection of pixels ≥130HU (blue, E) and the manual identification of MAC (purple, F). . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Patient demographics.

	Count	Percentage
Females	268	48%
NYHA III or IV	239	43%
Arterial hypertension	458	82%
Diabetes	149	27%
Dyslipidaemia	372	67%
Chronic obstructive pulmonary disease	66	12%
Cerebrovascular disease	114	20%
Peripheral artery disease	105	19%
Renal replacement or dialysis	14	3%
Chronic kidney disease KDIGO grade ≥3	291	52%
Mitral regurgitation (≥ moderate)	134	24%
Mitral stenosis (≥ mild)	24	4%
	Median	**IQR**
Age (years)	81	77–85
Body surface area (m^2)	1.83	1.67–1.97
Logistic EuroScore II	3.4	2.0–6.5

Abbreviations: KDIGO, kidney disease improving global outcomes; IQR, interquartile range; NYHA, New York Heart Association.

3.1. Subjective MAC assessment

Subjective MAC categorization among the four readers showed a substantial agreement (k = 0.67). Agreement for individual categories showed that the agreement for no MAC was nearly perfect (k = 0.88) and agreement for severe MAC was substantial (k = 0.75). However, agreement for mild (k = 0.45) and moderate (k = 0.59) MAC was only moderate. Table 2 shows the results of inter-reader MAC categorization. Intra-reader variability was substantial for both readers (reader 1, k = 0.69; reader 2, k = 0.62).

Table 2
Variability of subjective inter-reader assessment of MAC (n = 400).

	Reader 1	Reader 2	Reader 3	Reader 4
No MAC	106 (27%)	107 (27%)	118 (30%)	121 (30%)
Mild MAC	143 (36%)	141 (35%)	120 (30%)	132 (33%)
Moderate MAC	82 (21%)	84 (21%)	87 (22%)	77 (19%)
Severe MAC	69 (17%)	68 (17%)	75 (19%)	70 (18%)

Categorization shown as count (percentage).

3.2. Objective, quantitative MAC assessment

Evaluation of non-enhanced CT revealed 123 patients without MAC (22%) and 436 patients with MAC (78%). Objective, quantitative MAC assessment in patients with MAC showed a median Agatston_{MAC} score of 889 (IQR: 218-2′592; range: 2–18′281). A sex-specific analysis showed significantly more females than males (n = 227, 85% versus n = 209, 72%; $p < 0.001$) with MAC, with significantly higher Agatston_{MAC} scores in females compared to males (median 597, range 81-2′055 versus median 244; range 0–1′565; $p < 0.001$). An age-matched analysis showed that these differences were larger in patients ≥85 years (Fig. 2).

Inter- and intrareader agreement for quantitative MAC assessment using the Agatston method was excellent (ICC = 0.998 and ICC = 0.999, respectively). Fig. 3 illustrates the almost perfect agreement between two readers evaluating Agatston_{MAC} with minor inconsistencies in patients with extensive calcifications extending to the left ventricular outflow tract and/or aortic valve.

3.3. Comparison between subjective and objective MAC assessment

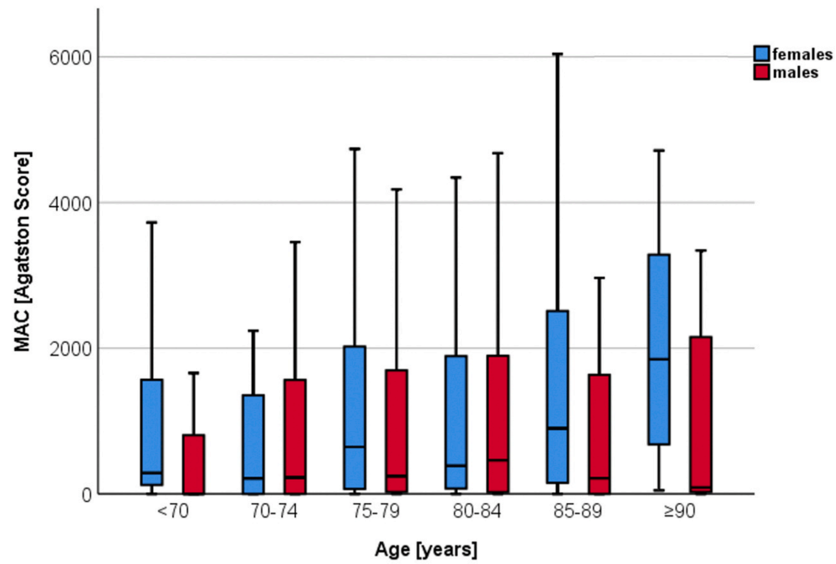
Fig. 4 shows the distribution of Agatston_{MAC} for each category of subjective MAC assessment with overlapping error bars between adjacent categories depending on calcification volume and density. Median Agatston_{MAC} scores for the subjective category “no MAC” was 0 (range: 0–11), 317 for “mild MAC” (range: 0–10′076), 1′829 for “moderate MAC” (range: 2–11′364), and 4′713 for “severe MAC” (range: 376-18′281).

3.4. Association of MAC with baseline patient characteristics

Patients with moderate or severe mitral regurgitation did not show a significantly higher Agatston_{MAC} compared to those with mild or no mitral regurgitation ($p = 0.10$; Table 3). Patients with mitral stenosis showed a significantly higher Agatston_{MAC} (median: 4′713, IQR: 1′660-10′396) compared to patients without mitral stenosis (median: 330, IQR: 16-1′703; $p < 0.001$; Table 3). Agatston_{MAC} shows an AUC of 0.84 (95% CI: 0.78–0.91) to diagnose mitral stenosis. Youden's index revealed that a Agatston_{MAC} cut-off-value of 1′406 has a sensitivity of 80% and specificity of 72% to diagnose mitral stenosis.

4. Discussion

The main results of our study are as follows: (1) subjective MAC assessment is prone to substantial intra- and interreader variability



Females	n	10	22	47	98	75	16
	Median	288	214	646	387	900	1849
	IQR	123-1567	0-1354	63-2095	73-1892	150-2553	681-3285
Males	n	37	40	67	86	48	13
	Median	0	226	244	463	215	89
	IQR:	0-805	0-1565	14-1829	24-1895	0-1635	27-2152

Fig. 2. Age- and sex-specific analysis of quantitative MAC. Note the higher Agatston$_{MAC}$ scores for females than for males particularly at ≥ 85 years of age.

particularly in cases with mild and moderate MAC; (2) inter- and intrareader variability of objective MAC assessment is almost perfect with only minor inconsistencies in patients with extensive MAC being in continuity with adjacent structures; (3) higher Agatston$_{MAC}$ scores are more frequent in women, with differences being pronounced in patients over 84 years of age; (4) Agatston$_{MAC}$ shows high accuracy to diagnose mitral stenosis, whereas there is no correlation of Agatston$_{MAC}$ with mitral regurgitation.

The mitral valve is a complex structure with a three-dimensional saddle shaped annulus.[25–27] CT can provide high-resolution, three-dimensional data for the evaluation of the mitral annulus including adjacent structures such as the circumflex artery and represents the imaging modality of choice for the evaluation of distribution and extent of MAC.[25,28] Quantitative evaluation of coronary artery and aortic valve calcifications on CT images with dedicated software platforms are easy to perform and are highly reproducible.[14,15] For the assessment of aortic valve calcifications, quantitative assessment has outperformed subjective assessment.[14,16] Quantitative calcification assessment not only allows for the differentiation between no, mild, moderate and severe aortic valve calcification but also allows to quantify different degrees of severe aortic valve calcification and allows to objectify sex-specific differences in valve calcifications.[14,16,29]

The presence of MAC has been related to a higher risk of cardiovascular events, cardiovascular death, and all-cause mortality.[5,6,9] For outcome studies, subjective semi-quantitative MAC assessment on contrast-enhanced CT with different methods were described,[5,6,17,18] which limit the comparability among these studies. Using one of these previously introduced subjective scoring systems[18] we found a substantial to almost perfect agreement between four readers in patients having either no or severe MAC. However, subjective assessment

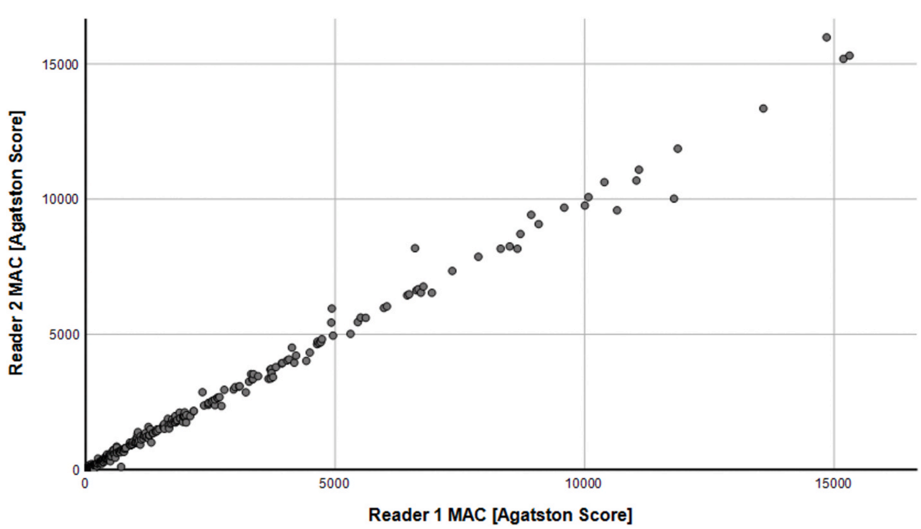


Fig. 3. Correlation of quantitative MAC between 2 readers. The scatter plot illustrates almost perfect agreement between two readers evaluating MAC in an objective quantitative manner using the Agatston Score ($r = 0.998$, $p < 0.001$).

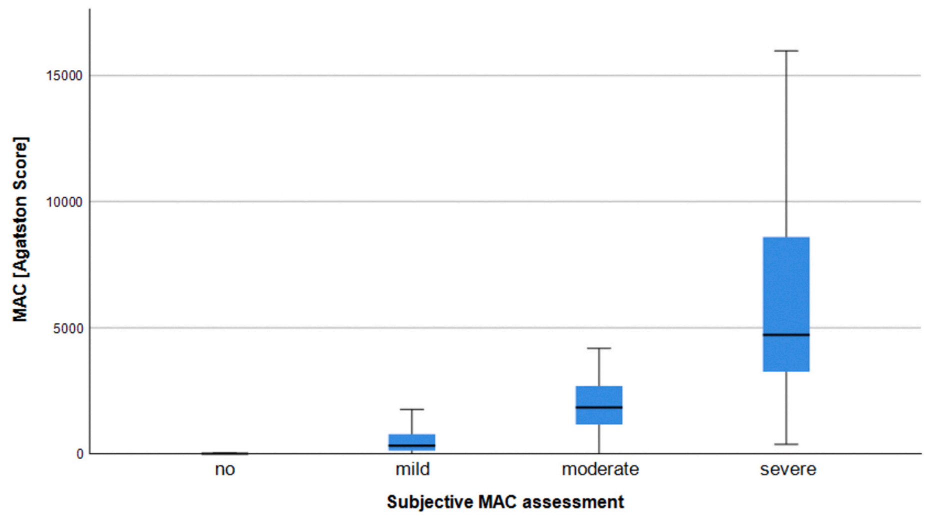


Fig. 4. Distribution of Agatston$_{MAC}$ between categories of subjective MAC assessment. The boxplots with large error bars indicating overlap of Agatston$_{MAC}$ scores between subjective MAC categories depending on calcification volume and density.

Table 3
Comparison of Agatston$_{MAC}$ with patient baseline characteristics.

		Agatston$_{MAC}$		p-value
		Median	IQR	
Sex	Female	597	81–2055	< **0.001**
	Male	244	0–1565	
NYHA III or IV	No	371	11–1828	0.48
	Yes	451	36–1894	
Arterial Hypertension	No	335	0–1882	0.76
	Yes	402	27–1846	
Diabetes	No	330	16–1798	0.11
	Yes	574	52–2460	
Dyslipidaemia	No	548	47–1950	0.11
	Yes	322	14–1746	
Chronic obstructive pulmonary disease	No	402	25–1829	0.96
	Yes	260	20–2851	
Cerebrovascular disease	No	389	17–1826	0.46
	Yes	396	52–1982	
Peripheral artery disease	No	352	24–1721	0.13
	Yes	548	50–2755	
Renal replacement or dialysis	No	422	26–2017	0.93
	Yes	362	203–1912	
Chronic kidney disease KDIGO grade ≥3	No	357	22–1831	0.58
	Yes	415	25–1934	
Mitral regurgitation (≥ moderate)	No	335	8–1827	0.10
	Yes	581	89–2095	
Mitral stenosis (≥ mild)	No	327	16–1721	< **0.001**
	Yes	4465	1535–10717	

Non-parametric, continuous variables are presented as median values with interquartile ranges (IQR) and were compared with the Mann-Whitney-U test.
Abbreviations: CABG, coronary artery bypass grafting; KDIGO, kidney disease improving global outcomes; IQR, interquartile range; MAC, mitral annular calcification; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

showed limited reproducibility in patients with mild and moderate MAC severity who represent the majority (52–57%) of patients in our study. On the contrary, quantitative MAC assessment was highly reproducible showing only minor inconsistencies between readers in patients with extensive calcifications extending beyond the mitral annulus to the left ventricular outflow tract and/or the aortic valve. In these patients, readers have to manually segment part of this continuous calcification and subjectively decided which part of the calcification belongs to the mitral annulus, resulting in minor inter- and intra-reader variability.

Quantitative MAC assessment may not only increase the reliability but also helps overcoming the problem of the lack of comparability between studies. A drawback of this method is the need for non-enhanced CT. However, this must be put into perspective considering the higher age of the population with MAC and the relatively low radiation dose needed to perform non-enhanced CT.[30] Furthermore, future studies may show that quantitative MAC assessment is possible also in contrast-enhanced CT, similar to previous reports in quantification of aortic valve or coronary calcification on contrast-enhanced CT.[30,31]

In contrast to aortic valve calcification showing higher Agatston scores in men than in women,[29] MAC is more frequent and more extensive in women.[8] Our results are in line with these previous findings showing higher Agatston$_{MAC}$ scores in women, particularly in patients ≥85 years of age.

In patients with MAC, an increased prevalence of both mitral regurgitation[7] and mitral stenosis[4] is described in the literature. Abramowitz et al.[5] described a similar frequency of mitral regurgitation in patients with and without MAC. Okuno et al.[4] found no relationship between subjective MAC grading and mitral regurgitation in patients with aortic stenosis, however, found a significant correlation between MAC severity and mitral stenosis. Our study shows similar results by demonstrating no significant differences in Agatston$_{MAC}$ scores between patients with relevant or no/mild mitral regurgitation. Furthermore, we found considerably higher Agatston$_{MAC}$ scores in patients with mitral stenosis than in those without.

4.1. Limitations

The following study limitations must be acknowledged. First, this was a retrospective single-center study with inherent limitations and possibility of selection bias. Second, in line with previous studies, subjective MAC assessment was performed on CT angiography image data. Reconstruction parameters in CT may influence the visibility of calcifications and different CT protocols may alter the visualization of calcifications, which was not assessed in this study. Third, we did not compare our quantitative results from CT with those from echocardiography. Fourth, our study cohort comprised patients with severe aortic stenosis planned to undergo TAVR. This limits generalizability of our results to other patient cohorts. Finally, our study lacks outcome data, and further research is warranted to assess whether quantitative MAC assessment is comparable or exceeds subjective MAC assessment for outcome prediction.

5. Conclusions

Our study in elderly patients with severe aortic stenosis shows considerable intra- and inter-reader variability of subjective MAC assessment which can be overcome with objective, quantitative MAC assessment using the Agatston method. The highly reliable quantitative MAC assessment should be evaluated in future outcome studies, having the potential to overcome previous limitations in the comparability of different subjective MAC assessments scores.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

Nothing to declare.

Acknowledgements

J.S. is a beneficiary of the Polish National Agency for Academic Exchange (NAWA) in 'The Iwanowska Programme' at the Department of Cardiology, MRI Cardiac Unit, University Hospital Zurich, Switzerland.

References

1. Elmariah S, Budoff MJ, Delaney JA, et al. Risk factors associated with the incidence and progression of mitral annulus calcification: the multi-ethnic study of atherosclerosis. *Am Heart J.* 2013;166:904–912.
2. Barasch E, Gottdiener JS, Larsen EK, Chaves PH, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and aortosclerosis in community dwelling elderly. The Cardiovascular Health Study (CHS). *Am Heart J.* 2006;151:39–47.
3. Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. *Circulation.* 2006;113:861–866.
4. Okuno T, Asami M, Khan F, et al. Does isolated mitral annular calcification in the absence of mitral valve disease affect clinical outcomes after transcatheter aortic valve replacement? *Eur Heart J Cardiovasc Imag.* 2020;21(5):522–532. https://doi.org/10.1093/ehjci/jez208 PMID 31408104.
5. Abramowitz Y, Kazuno Y, Chakravarty T, et al. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement. *Eur Heart J.* 2017;38:1194–1203.
6. Ancona MB, Giannini F, Mangieri A, et al. Impact of mitral annular calcium on outcomes after transcatheter aortic valve implantation. *Am J Cardiol.* 2017;120:2233–2240.
7. Movahed MR, Saito Y, Ahmadi-Kashani M, Ebrahimi R. Mitral annulus calcification is associated with valvular and cardiac structural abnormalities. *Cardiovasc Ultrasound.* 2007;5:14.
8. Roberts WC. Morphologic features of the normal and abnormal mitral valve. *Am J Cardiol.* 1983;51:1005–1028.
9. Kohsaka S, Jin Z, Rundek T, et al. Impact of mitral annular calcification on cardiovascular events in a multiethnic community: the Northern Manhattan Study. *JACC Cardiovasc Imag.* 2008;1:617–623.
10. Ng CK, Punzengruber C, Pachinger O, et al. Valve repair in mitral regurgitation complicated by severe annulus calcification. *Ann Thorac Surg.* 2000;70:53–58.
11. Guerrero M, Urena M, Himbert D, et al. 1-Year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. *J Am Coll Cardiol.* 2018;71:1841–1853.
12. Blanke P, Park JK, Grayburn P, et al. Left ventricular access point determination for a coaxial approach to the mitral annular landing zone in transcatheter mitral valve replacement. *J Cardiovasc Comput Tomogr.* 2017;11:281–287.
13. Karady J, Ntalas I, Prendergast B, et al. Transcatheter mitral valve replacement in mitral annulus calcification - "The art of computer simulation. *J Cardiovasc Comput Tomogr.* 2018;12:153–157.
14. Eberhard M, Hinzpeter R, Polacin M, et al. Reproducibility of aortic valve calcification scoring with computed tomography - an interplatform analysis. *J Cardiovasc Comput Tomogr.* 2019;13:92–98.
15. Weininger M, Ritz KS, Schoepf UJ, et al. Interplatform reproducibility of CT coronary calcium scoring software. *Radiology.* 2012;265:70–77.
16. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr.* 2019;13:1–20.
17. Takami Y, Tajima K. Mitral annular calcification in patients undergoing aortic valve replacement for aortic valve stenosis. *Heart Ves.* 2016;31:183–188.
18. Amat-Santos IJ, Revilla A, Lopez J, et al. Value of CT in patients undergoing self-expandable TAVR to assess outcomes of concomitant mitral regurgitation. *JACC Cardiovasc Imag.* 2015;8:226–227.
19. Pawade T, Sheth T, Guzzetti E, Dweck MR, Clavel MA. Why and how to measure aortic valve calcification in patients with aortic stenosis. *JACC Cardiovasc Imag.* 2019;12:1835–1848.
20. Higashigaito K, Schmid T, Puippe G, Morsbach F, Lachat M, Seifert B, Pfammatter T, Alkadhi H, Husarik DB. CT Angiography of the Aorta: Prospective Evaluation of Individualized Low-Volume Contrast Media Protocols. Radiology. 2016 Sep;280(3):960-8. doi: 10.1148/radiol.2016151982. Epub 2016 Mar 2.PMID: 26937711.
21. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imag.* 2013;14:611–644.
22. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr.* 2009;10:1–25.
23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33:159–174.
24. Rosner B. *Fundamentals of Biostatistics.* sixth ed. Duxbury: Thomson Brooks/Cole; 2006.
25. Gordic S, Nguyen-Kim TD, Manka R, et al. Sizing the mitral annulus in healthy subjects and patients with mitral regurgitation: 2D versus 3D measurements from cardiac CT. *Int J Cardiovasc Imag.* 2014;30:389–398.
26. Banks T, Razeghi O, Ntalas I, et al. Automated quantification of mitral valve geometry on multi-slice computed tomography in patients with dilated cardiomyopathy - implications for transcatheter mitral valve replacement. *J Cardiovasc Comput Tomogr.* 2018;12:329–337.
27. Blanke P, Dvir D, Cheung A, et al. A simplified D-shaped model of the mitral annulus to facilitate CT-based sizing before transcatheter mitral valve implantation. *J Cardiovasc Comput Tomogr.* 2014;8:459–467.
28. Hinzpeter R, Eberhard M, Pozzoli A, et al. Dynamic anatomic relationship of the coronary arteries to the valves. Part 1: mitral annulus and circumflex artery. *EuroIntervention.* 2019;15:919–922.
29. Aggarwal SR, Clavel MA, Messika-Zeitoun D, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. *Circ Cardiovasc Imag.* 2013;6:40–47.
30. Eberhard M, Mastalerz M, Frauenfelder T, et al. Quantification of aortic valve calcification on contrast-enhanced CT of patients prior to transcatheter aortic valve implantation. *EuroIntervention.* 2017;13:921–927.
31. Mylonas I, Alam M, Amily N, et al. Quantifying coronary artery calcification from a contrast-enhanced cardiac computed tomography angiography study. *Eur Heart J Cardiovasc Imag.* 2014;15:210–215.